UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/660,302	09/12/2000	Gerardus Jacobus Antonius Maria Strous	4075US	6944

24247 7590 09/26/2003

TRASK BRITT
P.O. BOX 2550
SALT LAKE CITY, UT 84110

EXAMINER	
MCKELVEY, TERRY ALAN	
ART UNIT	**PAPER NUMBER**
1636	24

DATE MAILED: 09/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/660,302	STROUS ET AL.	
	Examiner	Art Unit	
	Terry A. McKelvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *3-7,12-21,24,25 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,8-11,22,23,26-33,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-2, 8-11, 22-23, 26-33, and 35-36 in Paper No. 22, filed 7/1/03 is acknowledged.

Claims 3-7, 12-21, 24-25, and 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 22.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

In the instant case, a non-initialed and non-dated alteration has been made to the name of (Roland) Govers.

Specification

A substitute specification without the claims is required pursuant to 37 CFR 1.125(a) because the amendment filed 9/12/00 was too extensive to be entered into the specification.

A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; and 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

Claim Objections

Claims 27-32 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 27-32 attempt to further limit the claims they depend on by use or administration limitations. Use and co-administration limitations do not appear to further limit the claims because those limitations do not appear to result in an actual, structural limitation to the pharmaceutical compositions. In other words, because the pharmaceutical composition are what is actually being claimed, then limitations to how they are used, administered, or what they are administered with does not appear to affect the actual compositions themselves and thus they are not further limited in the dependent claims.

Claim Rejections - 35 USC § 112

Claims 1-2, 8-11, 22-23, 26-33, and 35-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an inhibitor for regulating the availability or activity of a protein comprising a polypeptide that interferes with ubiquitin-proteasome system regulation of

cell surface receptors of a cell, a pharmaceutical composition comprising the inhibitor, and a method for controlling or up-regulating the availability or activity of a protein by use of the inhibitor (including a non-polypeptide inhibitor). Thus, the claims are drawn to a genus of compounds (and a genus of a method using them) that is defined only by their function.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, the only factor present in some of the claims is a slight structural limitation of the target site of the inhibitor, which is not a description of the actual structure of the inhibitor. The specification appears to indicate two types of preferred embodiments of the inhibitors are encompassed by the claimed invention: general proteasome inhibitors (which are encompassed in inhibitors used in the method claims of claims 1-2 and 8-9), such as MG132 and lactacystin, which are known and described in the prior art, and (for all claims) polypeptide inhibitors derived from, competes

with, or binds to an amino acid sequence located at or around a ubiquitin and/or ubiquitin/proteasome binding site. The second type of inhibitor is only described according to the target (or some unspecified derivation of the target), not the actual structure of the compounds encompassed by this type of inhibitor. The specification fails to describe the specific structure of even one compound of this type of inhibitor. Accordingly, in the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus which encompasses the second type of inhibitor.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of inhibitors, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity

or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the first type of inhibitors (essentially the prior art inhibitors which are specifically listed in the specification), but not the full breadth of the claims meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claims 1-2, 8-11, 22-23, 26-33, and 35-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a

way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)). These include: nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the quantity of experimentation necessary, the relative skill levels of those in the art, and the breadth of the claim. The most relevant Wands factors for evaluating the enablement of the instant rejection are discussed below.

The claims are drawn to an inhibitor for regulating the availability or activity of a protein comprising a polypeptide that interferes with ubiquitin-proteasome system regulation of cell surface receptors of a cell, a pharmaceutical composition comprising the inhibitor, and a method for controlling or up-regulating the availability or activity of a protein by use of the inhibitor (including a non-polypeptide inhibitor).

The nature of the invention is unpredictable because the specification does not set forth a description of the inhibitors as claimed, for the reasons described above.

The state of the prior art and predictability in the art is that polypeptide inhibitors based upon a polypeptide binding site are not predictable based upon the structure of the binding site, but instead must be determined empirically for any given protein or protein system because protein structures are not predictable from a function or activity of the protein in the absence of additional information.

There are no working examples of polypeptide inhibitors as claimed in either the specification or the prior art.

Although there is some slight guidance concerning polypeptide inhibitors that are claimed: "polypeptide inhibitors derived from, competes with, or binds to an amino acid sequence located at or around a ubiquitin and/or ubiquitin/proteasome binding site", this guidance is negligible because it is not guidance to the actual structures of the polypeptide inhibitors as claimed, but instead it is guidance to the compounds that are to be tested for activity, and as such, it is not actual guidance as to how to make the claimed inhibitors.

Therefore, in order to make the claimed invention, which is also needed for using the claimed invention, one skilled in the art would have to perform unpredictable experimentation to make the claimed inhibitors because neither the art nor the

specification teaches a description of the inhibitors, from among the essentially unlimited number of possible polypeptides such that one can make the claimed invention. Such unpredictable experimentation would be undue in the absence of any description of the structures of the claimed inhibitors and in view of the state of the art and unpredictability in the art.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The claims are drawn to a pharmaceutical composition comprising a polypeptide inhibitors which interferes with ubiquitin-proteasome system regulation of cell surface receptors of a cell, which, from the specification, said polypeptides are derived from, competes with, or binds to an amino acid sequence

located at or around a ubiquitin and/or ubiquitin/proteasome binding site.

The only disclosed use for these compositions is for treatment of hormonal related or other diseases, such as treating patients with hormone deficiencies, or for treating muscle wasting caused by many different diseases.

The nature of the invention is very complex because it is a composition that is to be used to treat hormonal-related illness. Hormonal regulation in organisms is a very complex process which affects many different parts of the organism's body. Although there exists some treatments for some hormonal-related diseases, such as hormonal replacement therapy, there are no general or specific treatments based upon administration of a polypeptide that binds to a ubiquitin-proteasome system binding site.

The state of the prior art is that there is no teaching in the prior art of the same type of polypeptide inhibitors to treat any disease, let alone complex hormone related diseases.

Neither the art nor the specification teaches a working example of administration of the claimed pharmaceutical composition to a patient that successfully treats any disease.

There is no guidance in the prior art and only slight, prophetic generic guidance in the specification concerning how

to make and administer the claimed composition to treat disease. The specification merely teaches to administer the claimed polypeptide inhibitor, such as along with hormone treatment. The specification does not disclose, beyond a very generic description, the intended patients, and amounts of the composition to be administered for specific diseases. For example, the specification fails to teach how to specifically make and use the claimed composition for the treatment of muscle wasting versus treatment of hormonal deficiency, such as estrogen deficiency, two very different diseases that presumably would require very different pharmaceutical formulations and administration methods. This overall guidance is very slight because it can be considered to be merely speculative because the effective use of a compound having in vitro biological activity, as a drug to treat a disease, is extremely unpredictable as taught by Caldwell.

Caldwell is cited to show the unpredictability in the art concerning how to make and use a drug. Caldwell teaches that drug action is the result of interaction with target sites, for both desired and undesired actions, modulated by the transfer processes, the pharmacokinetic variables of absorption, distribution, metabolism and elimination, by which the drug enters and leaves the body. This reference teaches that there

is far more inter- and intraspecies variation, in animals and humans, in the factors influencing the nature and extent of internal exposure, than in the sensitivity of drug targets and this pharmacokinetic variability is the cause of major problems in drug development. Caldwell also teaches that failure to take these pharmacokinetic defects, including poor absorption, very short or very long half-life, enzyme induction and high first pass effect, into consideration can cause expensive delay and/or failure during development. This reference thus shows that drug development is very unpredictable, requiring the consideration of many unpredictable factors in determining how to make and use the drug. These very necessary, but unpredictable factors are not taught in either the art or the specification for the specific administration of the claimed composition in vivo for disease treatment, the only intended use for the claimed pharmaceutical compositions.

In view of the large quantity of experimentation necessary to determine the unpredictable parameters necessary for the pharmaceutical composition to function successfully in vivo, the lack of significant direction or guidance presented, the absence of working examples, the breadth of the claims which includes the treatment of very different diseases, and the unpredictable and undeveloped state of the art with respect to formulating a

polypeptide that affects the ubiquitin-proteasome system regulation of cell surface receptors of a cell into a functional drug that can treat a specific disease in vivo, it would require undue experimentation for one skilled in the art to practice the claimed invention.

Amending the claim to recite "A composition comprising ... " (i.e., removing reference to pharmaceutical), would be remedial in overcoming only the instant rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly

or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-2 and 8-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Fenteany et al (U.S. Patent No. 5,756,764).

Fenteany et al teach compounds related to lactacystin and lactacystin beta-lactone and pharmaceutical compositions containing the compounds (columns 1-11). This reference teaches that these compounds are highly selective inhibitors of the X/MB1 subunit and alpha-chain of the proteasome (column 11), which proteasome degrades or processes ubiquitin-conjugated proteins (column 1). Fenteany et al teach administration of the compounds to cells which blocked TNF-alpha dependent degradation of IkB-alpha (column 68) which administration inherently controlled the availability or activity of a protein by regulating binding of a ubiquitin-proteasome system at a ubiquitin-proteasome binding site of the protein because inhibition of the proteasome affects how much proteasome is bound at a ubiquitin-proteasome binding site of the protein (and thus regulates binding). In other words, by inhibiting the proteasome, administration of the compounds taught by the reference inherently affected the availability or activity of

all proteins that are regulated by the proteasome-ubiquitin system, including transporter proteins such as Glut4 insulin regulated glucose transporter. The inherency of the reference teaching the claimed invention is also shown by applicant's admission (e.g. page 9 of the specification) that preferred embodiments of the claimed inhibitor include proteasome inhibitors such as lactacystin. The additional limitation of the claim drawn to the ubiquitin-proteasome binding site is inherent because that is the binding site that is naturally used in the ubiquitin-proteasome system.

Claims 1-2 and 8-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al (Applicant reference marked as AA1 by the examiner).

Lee et al teach selective inhibitors of the proteasome-dependent pathway of protein degradation, and administration of those inhibitors to cells (abstract) which inherently controlled the availability or activity of a protein by regulating binding of a ubiquitin-proteasome system at a ubiquitin-proteasome binding site of the protein because inhibition of the proteasome affects how much proteasome is bound at a ubiquitin-proteasome binding site of the protein (and thus regulates binding). In other words, by inhibiting the proteasome, administration of the

compounds taught by the reference inherently affected the availability or activity of all proteins that are regulated by the proteasome-ubiquitin system, including transporter proteins such as Glut4 insulin regulated glucose transporter. The inherency of the reference teaching the claimed invention is also shown by applicant's admission (e.g. page 9 of the specification) that preferred embodiments of the claimed inhibitor include proteasome inhibitors such as lactacystin. The additional limitation of the claim drawn to the ubiquitin-proteasome binding site is inherent because that is the binding site that is naturally used in the ubiquitin-proteasome system.

Conclusion

No claims are allowed.

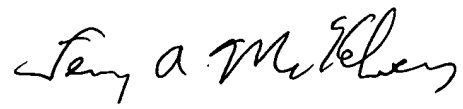
Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is 703-872-9306. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO

DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

September 23, 2003